

Background Management of acute pain in elderly patients in the Emergency Department is associated with a set of unique challenges that complicate care of these patients and at times lead to suboptimal pain relief. Age-related changes in drug absorption, metabolism and clearance as well as polypharmacy leading to dangerous drug-drug interactions place elderly patients at significant risks of drug-related side effects and even treatment failures related to frequent use of opioids and NSAID's. To complicate the issue of geriatric pain management even further, data shows that elderly patients are less likely to receive opioid analgesia or receive an appropriate dose of opioids both in the ED and on discharge in comparison to their younger counterparts.⁹⁻¹¹ Thus, in order to provide timely, effective and safe pain control for elderly patients, ED clinicians might consider exploring the utilization of non-opioid/non-NSAID-based analgesic modalities that have potential to provide comparable or even better pain relief than opioids and NSAID's but with lower rates of serious side effects. One such analgesic modality is subdissociative-dose ketamine (SDK).

Importance Ketamine is a non-competitive N-methyl-D-aspartate (NMDA)/glutamate receptor complex antagonist that decreases pain by diminishing central sensitization, hyperalgesia, and "wind-up" phenomenon at the level of the spinal cord (dorsal ganglion) and central nervous system. Ketamine administration in subdissociative doses (0.1-0.3 mg/kg) in pre-hospital settings and in the ED results in effective pain relief in patients with acute traumatic and non-traumatic pain, chronic non-cancer and cancer pain, and in patients with opioid-tolerant pain by virtue of providing anti-hyperalgesia, anti-allodynia, and anti-tolerance. Two commonly employed strategies of SDK administration in the ED include an intravenous push (IVP) dose (over 2-5 minutes), which is associated with relatively high rates of minor but bothersome psychoperceptual side effects (feeling of unreality and dizziness), or short infusion (SI) given over 15 minutes with significantly reduced rates of unreality and preserved analgesic efficacy. To our knowledge, there are no prospective randomized trials that evaluated SDK role in managing a variety of acute and chronic painful conditions in geriatric patients in the ED.

Goals of This Investigation In our study we hypothesize that an intravenous subdissociative-dose ketamine administered as a single agent in a dose of 0.3 mg/kg via short infusion over 15 minutes, will provide pain relief similar to that of intravenous morphine at 0.1 mg/kg administered over 15 minutes in geriatric ED patients with acute pain of moderate-to-severe intensity. The primary outcome of this trial is the comparative reduction in participant's pain scores at 30 minutes post medication administration.

MATERIALS AND METHODS

Study Design This will be a prospective, randomized, double-blind trial comparing the analgesic efficacy and safety of intravenous SDK with intravenous morphine both administered as a short infusion (over 15min) for acute pain in elderly ED patients. This study was approved by the Maimonides Medical Center institutional review board. The study will be conducted and is reported according to the Consolidated Standards of Reporting Trials Group.²³

Study Setting and Selection of Participants The study facility is a 711-bed community teaching hospital with an annual ED census of more than 120,000 visits. Patient screening, enrollment, and data collection were performed by a study investigator (S.M., J.D., and M.B.). ED pharmacy investigators will maintain the randomization list, which was generated before commencement of the study, prepared the medication, and delivered it to the nurse caring for the study participant in a blinded fashion. A convenience sample of patients will be enrolled between April 2016 and February 2018. Enrollment occurred at various times of the day when both a study investigator was available for patient enrollment and an ED pharmacist was available for medication preparation. The study will include patients aged 65 and older who present to the ED with acute abdominal, flank, back, or musculoskeletal pain with a score of 5 or more on a standard 11-point (0 to 10) numeric rating scale and required opioid analgesia, as determined by the treating attending physician. Acute pain is defined as having an onset within 7 days. Exclusion criteria includes altered mental status, allergy to morphine or ketamine, weight less than 40 kg or greater than 115 kg, unstable vital signs (systolic blood pressure <90 or >180 mm Hg, pulse rate <50 or >150 beats/min, and respiration rate <10 or >30 breaths/min), and past medical history of acute head or eye injury, seizure, intracranial hypertension, severe chronic

obstructive pulmonary disease, chronic pain, renal or hepatic insufficiency, alcohol or drug abuse, psychiatric illness, or recent (4 hours before) opioid use. Each patient will be approached by a study investigator for acquisition of written informed consent and Health Insurance Portability and Accountability Act authorization after being evaluated by the treating emergency physician and determined to meet study eligibility criteria. When English is not the participant's primary language, a staff interpreter or licensed telephone interpreter will be used. Baseline pain score will be determined with an 11-point numeric rating scale (0 to 10), described to the patient as "no pain" being 0 and "the worst pain imaginable" being 10. A patient will be eligible for enrollment if a baseline numeric rating scale score of 5 or greater is reported. A study investigator will then record the patient's body weight and baseline vital signs. The on-duty ED pharmacist will prepare 0.3 mg/kg of ketamine or 0.1 mg/kg of morphine in 100 mL of normal saline solution according to the predetermined randomization list, which is created in SPSS (version 24; IBM Corp, Armonk, NY) with block randomization of every 10 participants.

We based our decision to utilize short infusion of either analgesics instead of intravenous push on the prior research (SDK) and clinical experience (morphine) that demonstrated a lesser degree of psychoperceptual side effects and preserved analgesic efficacy of SDK and lesser degree of nausea and lightheadedness of morphine. The medication will be delivered to the treating nurse in a blinded fashion and was administered by short intravenous infusion over 15 min via an infusion pump.

The preparing pharmacist, research manager, and statistician will be the only members of the team with knowledge of the study arm to which the participant will be randomized, leaving the providers, participants, and data collecting research team blinded to the medication received.

Study investigators will record pain scores, vital signs, and adverse effects at 15, 30, 60, 90, and 120 minutes. If patients reported a pain numeric rating scale score of 5 or greater and requested additional pain relief, fentanyl at 0.5 mcg/kg was administered as a rescue analgesic. Blinding of the patient, research team, and clinical staff will be strictly maintained by the on-duty ED pharmacist. All data recorded on data collection sheets, including patients sex, demographics, medical history, and vital signs, will be entered into SPSS (version 24.0; IBM Corp) by the research manager. Development of the randomization list, confirmation of written consent acquisition for all participants, and statistical analyses will be conducted by the research manager and statistician, who will work independent of any data collection.

Outcome Measures: The primary outcome is a comparative reduction of pain scores on numeric rating pain scale (NRS) between recipients of SDK and morphine at 30 minutes.

Data Analyses Plan Data analyses included frequency distributions, paired t-test to assess a difference in pain scores within each group, and independent-sample t-test to assess differences in pain scores between the 2 groups at the various intervals (SPSS, version 24; IBM Corp). Mixed-model linear regression (SAS, version 9.4; SAS Institute, Inc., Cary, NC) will be used to compare changes in pain numeric rating scale across time points. This compensated for participants lost to follow-up and allowed all patients' data to be analyzed on an intention-to-treat principle. For categorical outcomes (eg, complete resolution of pain), a χ^2 or Fisher's exact test was used to compare rates for categorical outcomes at 30 minutes. Percentage differences and 95% confidence intervals between the treatment groups were calculated for all time points. $P < .05$ was used to denote statistical significance. Based on the validation of a verbally administered rating scale of acute pain in the ED and the comparison of verbal and visual pain scales, we used a primary outcome consisting of a minimal clinically meaningful difference of 1.3 between the SDK and morphine groups at the 30-minute pain assessment.